linked to schizophrenia. We will present data from a group of 45 SPD subjects who were assessed on a specific set of information processing tasks including startle prepulse inhibition, P50 event related potential sensory gating, visual backward masking, visual contrast sensitivity, ocular motor measurement, choice, and neuropsychological measures. Preliminary analyses show strong but selective relationships between many of the information processing measures. These results suggest that some of the measures may collectively identify a vulnerability to schizophrenia. In addition, there appear to be subgroups of SPD subjects with deficits across multiple measures. The significance of these findings will be discussed.

118. PPI IN UNMEDICATED AND MEDICATED ACUTELY PSYCHOTIC SCHIZOPHRENIA PATIENTS

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The present study was designed to extend our understanding of sensorimotor gating in acutely psychotic schizophrenia patients and to assess the relationship between gating deficits and neuroleptic treatment. Many studies support the hypothesis of a schizophrenia-linked deficit in sensorimotor gating with an associated vulnerability to psychosis. One way to assess sensorimotor gating in humans is through prepulse inhibition (PPI) of the startle blink reflex. PPI occurs when a weak prestimulus presented 30 to 500 milliseconds prior to a startling stimulus results in a dampening of the blink reflex. In animal studies, activation of D2 dopamine function in the limbic forebrain produces deficits in PPI that model the PPI deficits seen in schizophrenia patients. Blockade of the D2 receptors restores prepulse inhibition. Recently, there has been a report that clozapine-treated schizophrenia patients showed normal levels of PPI compared to patients treated with typical neuroleptics. The same group has also found that haloperidol disrupted PPI in normal males leading to the conclusion that hypo and hyperdopaminergic states may lead to PPI deficits. However, it remains unclear if there is an interaction between medication status, acuity and symptom state in the mediation of PPI. The strategy used in this study to address this question was to assess a sample of schizophrenia patients all of whom are within 48 hours of admission to an acute psychiatric hospital.

In this study, PPI was measured in acutely psychotic schizophrenia patients within 48 hours of admission. Sixteen patients were unmedicated while the other 13 were being treated with an antipsychotic medication, eleven patients were treated with atypical antipsychotic medications. Subjects were clinically assessed with the PANSS to quantify symptoms. The medicated versus unmedicated subjects were not significantly different on any of the symptom measures. PPI was measured in a paradigm using three prepulse to pulse intervals (30, 60 and 120 msecs). There were no differences between the two groups for any of the three conditions, nor was there a relationship between symptoms and PPI for either group or when the groups were combined. These findings support the interpretation that symptom acuity is a more powerful mediator of PPI than medication status in schizophrenia patients.

119. SUSTAINED HALOPERIDOL OPPOSES APOMORPHINE AND PHENCYCLIDINE-INDUCED STARTLE GATING DEFICITS

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Both dopamine (DA) agonists and NMDA antagonists produce prepulse inhibition (PPI) deficits in rats that model PPI deficits in schizophrenia patients. While DA agonist effects on PPI are reversed by acute treatment with either “typical” high potency D2 DA antagonists or “atypical” antipsychotics, PPI deficits produced by phencyclidine (PCP) are preferentially reversed by acute treatment with “atypical” antipsychotics. Acute effects of antipsychotics may not accurately model the more clinically relevant effects of these drugs, that emerge after several weeks of continuous treatment. In the present study, sustained treatment with haloperidol via subcutaneous minipumps blocked the PPI-disruptive effects of the DA agonist apomorphine and attenuated the PCP-induced disruption of PPI. Restoration of PPI in apomorphine-treated rats was evident within the first week of sustained haloperidol administration; a partial but statistically significant reversal of PCP effects on PPI did not develop until weeks 2–3 of haloperidol treatment, was not observed for treatment weeks 4–6, then re-emerged in the seventh week of sustained haloperidol treatment. The delayed emergence and re-emergence of anti-PCP effects of haloperidol suggests that the brain substrates responsible for the DAergic and NMDA regulation of PPI are differentially sensitive to acute and chronic effects of antipsychotics. Supported by MH 01436 and MH 58384.

120. REGULATION OF SENSORIMOTOR GATING IN RATS BY HIPPOCAMPAL NMDA: ANATOMICAL LOCALIZATION

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Prepulse inhibition (PPI) of the startle reflex is a measure of sensorimotor gating that is reduced in humans with certain neuropsychiatric disorders, including schizophrenia, and in rats after manipulations of limbic cortico-striato-pallido-pontine circuitry. We have reported that PPI is reduced after specific manipulations of the hippocampal complex (HPC) in rats, but the mechanisms for these effects remain poorly understood. For example, dopaminergic substrates clearly regulate PPI, but the PPI-disruptive effects of intra-HPC carbachol or NMDA are not reversed by D2 receptor antagonists. This study examined the anatomical specificity within the HPC of the PPI-disruptive effects of NMDA infusion. Startle magnitude and PPI were assessed after acute bilateral infusion of NMDA (0, 0.4 or 0.8 μg) into the dorsal subiculum (DS), the ventral subiculum (VS) or the entorhinal cortex (EC), in a within-subject design with order balanced across groups. A dose-dependent disruption of PPI was observed after NMDA infusion into the VS or EC, but not the DS. These findings demonstrate the importance of the ventral, but not the dorsal HPC, in the glutamatergic regulation of PPI. The proximity of the VS and EC preclude simple conclusions regarding the relative role of...
these substrates in the PPI-disruptive effects of NMDA. Replication studies are in progress, as are studies designed to distinguish the contribution of the VS and EC to the PPI-disruptive effects of NMDA infusion within the HPC.

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121. TOWARDS THE GENETICS OF A COMPLEX PHENOTYPE: STRAIN ANALYSES OF DRUG EFFECTS ON STARTLE GATING


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Sensorimotor gating of the startle reflex, measured by PPI, is impaired in humans with specific neuropsychiatric disorders, and is disrupted in humans and rats by dopamine (DA) agonists. Animal models are clarifying the genetics of PPI and its sensitivity to biochemical regulation. Differences in sensitivity to the PPI-disruptive effects of APO across rat strains (eg. Sprague Dawley (SD) vs. Wistar (W)), and within strains, across suppliers (eg. Harlan ["H"] vs. Bantin-Kingman ["BK"]) must reflect relatively subtle genetic drift, which might be manipulated by pharmacogenetic strategies and serve as targets for QTL or other approaches for understanding the genetics of complex phenotypes.

We assessed the scope and development of PPI APO sensitivity differences in SD vs. W rats (H and BK). Findings confirmed significant SDH > WH sensitivity to the PPI-disruptive effects of APO in adults and d18 pups; an SDH x WH F1 exhibited the WH parental phenotype. Both BK rat strains were less sensitive than SDH rats to the PPI-disruptive effects of APO; in SDBKs, APO effects on PPI interacted with changes in startle magnitude. SDH > SDBK sensitivity was also noted in the PPI-disruptive effects of the D1 agonist SKF82958, but not the D2 agonist quinpirole. Substrain differences in PPI drug sensitivity are DA receptor subtype-specific. SDH > WH APO sensitivity in d18 pups suggests that genetic differences in DAergic sensitivity are expressed early in development; for this substrate, efficient phenotype screening can be completed in pups.

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122. EFFECTS OF CAFFEINE ON SENSORIMOTOR GATING OF THE STARTLE REFLEX IN NORMAL CONTROL SUBJECTS


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Prepulse inhibition (PPI), a cross-species measure of sensorimotor gating, is impaired in certain neuropsychiatric disorders. This study was designed to assess caffeine effects on PPI in normal humans, as part of an effort to understand cross-species differences and similarities in the neurochemical regulation of PPI. Startle was measured during a screening session (“DAY 1”); 7–10d later, subjects were retested (“DAY 2”) after placebo or caffeine (200 mg; double-blind design). Subjects, characterized as low vs. high caffeine drinkers (LOCAF vs. HICAF) based on established scales, refrained from ad libitum caffeine consumption for ≥ 15h prior to DAY 2 testing. Autonomic and self-rating measures, acoustic and tactile startle, and unimodal and cross-modal PPI, were measured in divided sessions for 3h post-treatment. On DAY 2, there were significant effects of caffeine on autonomic measures but not acoustic or tactile startle magnitude, habituation or PPI. HICAF subjects reported withdrawal symptoms after placebo that were blunted by caffeine. Compared to DAY 1 measures, DAY 2 PPI was greater in LOCAF subjects after placebo, and in HICAF subjects after caffeine. The opposite pattern was also true: LOCAF subjects exhibited less PPI after caffeine, and HICAF subjects exhibited less PPI after placebo, on DAY 2 vs. DAY 1. Thus, caffeine withdrawal, evident in HICAF subjects after placebo, may be accompanied by reduced PPI. A new study is in progress in which subjects maintain ad libitum caffeine intake to blunt any impact of caffeine withdrawal on startle.

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123. CEREBELLAR GRAY MATTER VOLUME DEFICITS IN SCHIZOPHRENIA AND ALCOHOLISM


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Cerebellar pathology may contribute to the pathophysiology of schizophrenia, yet it remains controversial whether cerebellar dysmorphology occurs in schizophrenia and, if it does, what specifically is affected. Complicating this search is the high incidence of alcohol abuse in schizophrenia that can contribute to cerebellar pathology, most notably in anterior superior vermis.

To examine these issues, we used thin-slice, 3D MRI to study normal control men (NC), 25 alcoholic men (ALC), 27 schizophrenic men (SZ), and 19 men comorbid for schizophrenia and alcohol abuse (SZ + ALC). Cerebellar structures were manually outlined, tissue classification was statistically determined, and regional volumes were corrected for normal variation in head size and age. SZ had enlarged fourth ventricles but not cerebellar tissue volume deficits. ALC had smaller cerebellar volume deficits (most prominent in the anterior superior lobules) and gray matter hemisphere deficits, but not fourth ventricle enlargement. SZ + ALC had cerebellar hemisphere and vermis gray matter volume deficits and fourth ventricular enlargement to a greater extent than did either single diagnosis group, despite relatively low levels of alcohol consumption of the SZ + ALC compared to the ALC group. Gray matter volume in the anterior superior vermis correlated with lifetime alcohol consumption in the total group of schizophrenic patients. These data support the contention that even relatively modest levels of alcohol consumption is a major factor underlying cerebellar volume deficits in schizophrenia. Consequently, schizophrenics may have cerebellar supersensitivity to the detrimental effects of alcohol, with added risk of motor and cognitive dysfunction common to both diseases.

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